REMARKS

Claims 102, 105, and 106 are under consideration. Claims 102 and 105 have been amended. Support for the amendments may be found throughout the specification, for example, at Figure 4, [0135] to [0138], and [0140] to [0141] of corresponding Publication No. 2004/0127416. The amendments add no new matter and entry is requested.

Rejection under 35 U.S.C. § 103

On page 3 of the Office Action mailed August 3, 2010, the Examiner rejects claims 102, 105 and 106, under 35 U.S.C. § 103(a), "as being unpatentable over Rieu et al (Journal Cell Biology 1994 v127 pages 2081-2091 ...) and Laplantine et al (Journal of Cell Science 2000 v113 1167-1176)..." Applicants traverse the rejection.

The claimed invention provides for a therapeutic bioconjugate that inhibits inflammatory cell adhesion consisting of a hydrophilic polymer cross-linked to a peptide having the amino acid sequence Cys Asn Ala Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu Lys (SEQ ID NO:124); wherein the peptide of said therapeutic bioconjugate binds to a cell expressing an intercellular adhesion molecule (ICAM) and the hydrophilic polymer inhibits monocyte adhesion to said cell; and wherein the degree of inhibition of monocyte adhesion by said bioconjugate is at least five-times that of said peptide alone.

The amended claims clarify the nature of the claimed composition as a bioconjugate that has the novel and unexpected features of inhibiting inflammatory cell adhesion. Both the preamble and the limitations of claims 102 and 105 provide for a therapeutic bioconjugate for inhibiting inflammatory cell adhesion, specifically by a hydrophilic polymer cross-linked to a peptide wherein the peptide binds to a cell expressing an ICAM and the hydrophilic polymer inhibits monocyte adhesion to the cell; and wherein the degree of inhibition of monocyte adhesion by the bioconjugate is at least five-times that of the peptide alone.

The Examiner stated, on page 10, that "Whether or not the product is used for Plasmon resonance or any other application dose not appear to be relevant." This assertion is incorrect as a matter of law.

That the claims relate to a "product" does not negate the relevance to the claims of the recited function, which is unknown in the art, based on the presence of some other claimed elements allegedly suggested in the cited art. For example, "[A] claim preamble has the import that the claim as a whole suggests for it." *Bell Commun. Res., Inc. v. Vitalink Commun. Corp.*, 55 F.3d 615, 620

(Fed. Cir. 1995). "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). *See also Kropa v. Robie*, 187 F.2d 150, 152 (CCPA 1951) (preamble reciting "An abrasive article" was deemed essential to point out the invention defined by claims to an article comprising abrasive grains and a hardened binder and the process of making it. The court stated "it is only by that phrase that it can be known that the subject matter defined by the claims is comprised as an abrasive article. Every union of substances capable *inter alia* of use as abrasive grains and a binder is not an 'abrasive article.'" Therefore, the preamble served to further define the structure of the article). *See also In re Stencel*, 828 F.2d 751, 754 (Fed. Cir. 1987). ("[T]he framework - the teachings of the prior art - against which patentability is measured is not all drivers broadly, but drivers suitable for use in combination with this collar, for the claims are so limited.").

The instant preamble does, in fact, provide a distinct definition of the claimed invention's limitations : the bioconjugate inhibits inflammatory cell adhesion. Only if a prior art structure is capable of performing the intended use as recited in the preamble does it meets the claim. *See, e.g., In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). *In Poly-America LP v. GSE Lining Tech. Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004), the court stated that "the preamble language relating to 'blown-film' does not state a purpose or an intended use of the invention, but rather discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim." In this light, when applied to the pending claims, the question is whether the cited art taught the intended use of the bioconjugate as an inhibitor of inflammatory cell adhesion. As explained further herein, the answer is no.

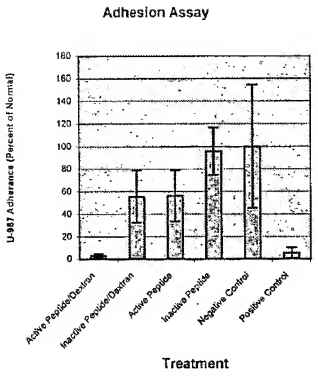
Similarly, the determination of whether a "wherein" clause is a limitation in a claim depends on the specific facts of the case. The Court held in *In Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, (Fed. Cir. 2005), that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." In the pending claims, the Examiner may not ignore the limitations related to patentability that serve to change the substance of the claimed invention, for example, from a peptide containing an additional N-terminal cysteine immobilized a sensor chip via dextran for Plasmon resonance to a bioconjugate whereby the peptide binds to a cell expressing an intercellular adhesion molecule and the hydrophilic polymer inhibits monocyte adhesion to said cell; and wherein the degree of inhibition of monocyte

adhesion by said bioconjugate is at least five-times that of said peptide alone. For example, there is nothing in the combined art suggesting that the hydrophilic polymer as recited in the claimed invention inhibits monocyte adhesion to the cell.

The Examiner states, on page 6 of the action, "that there is a reasonable basis that the polysaccharide has the recited function." There is simply no support in the cited art for this conclusion. Neither Rieu nor Laplantine teach or suggest that the hydrophilic polymer inhibits monocyte adhesion to the cell. Laplantine refers to peptides containing an additional N-terminal cysteine immobilized by dextran on a sensor chip for Plasmon resonance, not for inhibiting monocyte/cell adhesion.

Rieu refers to the binding site for neutrophil adhesion inhibitor (NIF) in β2 integrin complement receptor type 3 (CD11b/CD18). The Examiner notes, on page 8 of the Action, that A7 peptide was found to bind iC3b. But if A7 had the required inhibitory activity of the instant claims, where is the motivation to one of skill in the art to cross-link it to a polysaccharide for that purpose? Such motivation is not provided by a reference (Laplantine) to a peptide containing an additional N-terminal cysteine immobilized by dextran on a sensor chip for Plasmon resonance. Additionally, the dextran-bound compositions of Laplantine included a sensor chip that is not included in the claimed invention consisting of a peptide cross-linked to a hydrophilic polymer that inhibits monocyte adhesion. Put simply, when dextran is attached to a sensor chip there is no suggestion that the dextran will inhibit adhesion between a leukocyte and a cell that expresses ICAM. Moreover, when dextran is attached to a sensor chip there is no suggestion it can act as a therapeutic biogojugate.

On page 9 of the Action, the Examiner noted that the previous claims had not recited any degree of inhibition. The amended claims relate to the unexpected and synergistic activity of the bioconjugate. Indeed, the synergism is evidenced in Figure 4, in which the bioconjugate (labeled "Active Peptide/Dextran") showed more than five-fold inhibition over the un-conjugated peptide (labeled "Active Peptide"):



This result is further explained and supported in the text:

[0137] Referring to FIG. 4, the results of this assay illustrate the biospecific binding of the peptide/dextran conjugate to bovine endothelial cells. In this assay all but the positive control were activated with TNF-α to induce ICAM expression. The negative control represents 100%. Treatment with ***active peptide conjugate resulted in a relative monocyte adherence of 3.34±1.69%***. The positive control, where the endothelial cells were not induced, had monocyte adherence of 5.741±4.81%, which is not statistically different from samples where ICAM expression was induced preceding treatment with the active conjugate. The treatment with the inactive peptide conjugate yielded a relative adherence of 55.65±23.42%, while treatment with the active ***peptide alone led to a monocyte adherence of 56.28±22.67%***. The treatment with the inactive peptide alone was comparable to no treatment after the TNF-α activation. Inactive peptide treatment gave a relative monocyte adherence of 95.71±21.03%. The standard deviation for the negative control was 54.5.

[0138] The active dextran bioconjugate effectively bound to TNF-α stimulated, ICAM-expressing BECs and prevented monocyte adhesion to the extent observed in non-stimulated BECS (positive control). Unconjugated peptides, dextran, and the inactive peptide conjugate inhibited cell adhesion poorly, suggesting that only the combined effect of specific binding of active peptide conjugates to ICAM and formation of an ICAM-bound nonadhesive dextran layer promoted reduced monocyte adhesion to TNF-α stimulated, ICAM-expressing BECs. Since leukocyte/tissue adhesion plays a major role in a number of the pathological processes discussed above, these bioconjugates could be utilized as targeted therapeutics for many applications.

The Examiner asserts, on page 10, that there was motivation to combine the references because "both Rieu and Laplantine are drawn to methods of identifying interacting regions between integrins and interaction partners." The Examiner's assertion is no more than an invitation to try. In that regard:

> what would have been "obvious to try" would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices were likely to be successful. ... In others what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only ***general guidance*** as to the particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) (emphasis added).

The Examiner does not explain, for example, where Rieu or Laplantine provides a reasonable expectation of success that, *inter alia*, the claimed peptide cross-linked to a hydrophilic polymer whereby the hydrophilic polymer inhibits monocyte adhesion to an ICAM-expressing cell, and wherein the degree of inhibition of monocyte adhesion by the bioconjugate is at least five-times that of the peptide alone. ***There is nothing in Rieu or Laplantine regarding hydrophilic polymer inhibition of monocyte adhesion***, nor anything suggesting that the degree of inhibition of monocyte adhesion by the bioconjugate is at least five-times that of the peptide alone. Thus, Rieu and Laplantine do not suggest the claimed therapeutic consisting of the claimed peptide conjugated to a hydrophilic polymer, in which the peptide of the bioconjugate binds to a cell expressing ICAM and the hydrophilic polymer inhibits monocyte adhesion to that cell.

The Examiner states, on page 11, that "Although Applicants argue that the prior art does not teach that the polymer inhibits the binding of leukocytes to ICAM-expressing cells, it is noted that the claims do not refer to leukocytes." With all due respect, the claims refer to monocytes, which those of ordinary skill in the art are well aware are leukocytes. The simplest inquiry into the definition of monocyte would have educated the Examiner that a monocyte is a type of leukocyte: *see, e.g.*, http://medical-dictionary.thefreedictionary.com/monocyte+leukocyte.

Moreover, the present specification uses the terms, for example, as follows:

> [0140] To assess the effect of these peptide-dextran bioconjugates on inflammatory cell adhesion, the following in vitro ICAM-1-mediated leukocyte cell adhesion assay was performed. HUVEC monolayers were established in 24-well culture dishes. At 24 h prior to the assay, normal culture media were replaced with medium containing TNF-α (10 ng/ml). Following the 24 h incubation period, each sample well received a medium change. Treated sample groups received medium containing 6% dextran bioconjugate (dextran conjugated to

the A domain peptide CNAFKILVVITDGEK). Untreated control samples received normal medium. Negative sham control samples received medium containing dextran conjugate with a scrambled A domain sequence (KCENGADFTKIIVLV). All samples were then incubated for 30 min prior to the adhesion assay. Medium was removed from all wells following the 30 min incubation and replaced with medium containing U937 monocytic cells (1×10^5/ml). All samples were then incubated for another 30 min. After this incubation period, samples were washed three times with PBS to remove non-adherent monocytes. The samples were then fixed, and an average number of adherent monocytes per 100× microscopic field was determined for each sample group. Statistical comparisons between sample groups (n=4 replicate wells per group) were performed using a student's t-test.

Hence, there is no need to read limitations from the specification into the claims - the claims are quite specific in this regard.

The Court has instructed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). But the combination of Rieu and Laplantine does not even provide for each of the limitations of the pending claims: a therapeutic bioconjugate consisting of a peptide, CNAFKILVVITDGEK, cross-linked to a hydrophilic polymer, wherein the peptide binds to cells that express ICAM, and the polymer inhibits the binding of monocytes to those ICAM-expressing cells, and wherein the degree of inhibition of monocyte adhesion by said bioconjugate is at least five-times that of the peptide alone.

The Examiner asserts that "[Because] the experiments of Rieu were limited by the inability of certain peptides to bind one would be motivated to use other methods to test direct binding. As discussed …, Laplanitne teach such methods. One would have been motivated to combine the references to address the problem. Thus one would be motivated to address the problem set forth in Rieu." Office Action at pages 10-11. The nature of the problem to be solved was not "to test direct binding," however, but (as stated in the claims) to inhibit inflammatory cell adhesion by inhibiting monocyte adhesion. In other words, the claimed solution of inhibiting monocyte adhesion by the hydrophilic polymer of the cross-linked peptide-polymer conjugate is not the solution of direct peptide binding. Indeed, direct peptide binding was at least five-times less inhibitory than the that achieved by the claimed bioconjugate.

Hence, Applicants urge that the combination of Rieu and Palantine do not support a § 103 rejection, and request that this rejection be withdrawn.

CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. The Commissioner is hereby authorized to charge any payment deficiency to Deposit Account No. 19-2380 referring to Attorney Docket No. 049954-004100. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Should the Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicants' representative designated below.

Respectfully,

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/Mary S. Webster, Reg. No. 37,156/
Mary S. Webster
Reg. No. 37,156

Customer No. 22204
NIXON PEABODY LLP
Suite 900
401 9th Street, N.W.
Washington, DC 20004-2128
Telephone: (202) 585-8000
mwebster@nixonpeabody.com